Early survival and safety of ALPPS: first report of the International ALPPS Registry

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Abstract: OBJECTIVES To assess safety and outcomes of the novel 2-stage hepatectomy, Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS), using an international registry. BACKGROUND ALPPS induces accelerated growth of small future liver remnants (FLR) to allow curative resection of liver tumors. There is concern about safety based on reports of higher morbidity and mortality. METHODS A Web-based data entry system was created with password access and data pseudoencryption (NCT01924741). All patients with complete 90-day data were included. Multivariate logistic regression analysis was performed to identify independent risk factors for severe complications and mortality and volume growth of the FLR. RESULTS Complete data were available for 202 patients. A total of 141 (70%) patients had colorectal liver metastases (CRLM). Median starting standardized future liver remnants of 21% increased by 80% within a median of 7 days. Ninety-day mortality was 19/202 (9%). Severe complications including mortalities (Clavien-Dindo IIIb) occurred in 27% of patients. Independent factors for severe complications were red blood cell transfusion [odds ratio (OR), 5.2), ALPPS stage I operating time greater than 300 minutes (OR, 4.4), age more than 60 years (OR, 3.8), and non-CRLM (OR, 2.7). Age, use of Pringle maneuver, and histologic changes led to less volume growth. In patients younger than 60 years with CRLM, 90-day mortality was similar to conventional 2-stage hepatectomies for CRLM. CONCLUSIONS This is the first analysis of the ALPPS registry showing that ALPPS has increased perioperative morbidity and mortality in older patients but better outcomes in patients with CRLM.

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Early Survival and Safety of ALPPS

First Report of the International ALPPS Registry

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Conclusions: This is the first analysis of the ALPPS registry showing that ALPPS has increased perioperative morbidity and mortality in older patients but better outcomes in patients with CRLM.

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During the last decade, 2-stage hepatectomy was established as a curative treatment strategy for patients with initially unresectable bilobar liver tumors.[1] An element of this strategy is portal vein occlusion to induce hypertrophy of the future liver remnant (FLR). Recently, a novel variant of 2-stage hepatectomy, termed "Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy" (ALPPS), has been reported.[2] ALPPS induces faster hypertrophy of the FLR than the conventional 2-stage hepatectomy.[3] In addition to occlusion of the right portal vein and cleaning of the left liver from tumor, transection between the "deportalized" and the normally vascularized (FLR) parts of the liver is performed at stage I. Stage II follows with removal of the deportalized part of the liver after rapid hypertrophy of the FLR, usually within 7 to 10 days after stage I.[4] Since its introduction, ALPPS has been adopted by many surgeons worldwide.[4–10]

The initially reported mortality of 12%[2] triggered an intense debate about the safety of this procedure.[3,10–12] The international ALPPS registry was initiated in 2012 to systematically and uniformly collect information from multiple centers worldwide. The registry should enable surgeons to study a larger population to overcome shortcomings inherent to small case series reports.[13] Furthermore, the registry may help refine patients' selection for this complex procedure. The aim of this first analysis was to determine (1) perioperative morbidity and mortality, (2) independent predictors for poorer outcome, (3) overall survival and recurrence-free survival, and (4) independent predictors for the rapid hypertrophy of the FLR.

MATERIALS AND METHODS

Study Design and Study Setting

Ethics approval was obtained for an online registry at the Ethics Committee Kanton Zurich, Switzerland, and the study was registered at Clinicaltrials.gov (NCT01924741). To establish the registry, an electronic case report form using the clinical trials software SECUTRIAL (Interactive System, Berlin, Germany) was presented to selected experts worldwide for approval (Scientific Committee of the ALPPS Registry). Any center willing to report patients in the registry was given access through the Web page www.alpps.net. Pseudoencryption data for identification of patients are held by the centers. All coinvestigators involved in data entry are listed in the ALPPS registry group author section later. Data were entered between October 2012 and December 2013. Completeness of data entry was monitored through a query and answer system maintained by a dedicated study nurse in Zurich. Data auditing was performed on a weekly basis by

the registry administrators (E.S., V.A., D.R., and A.S.). Data export and analysis were performed in January 2014.

Participants and Variables

All patients undergoing ALPPS were eligible. Centers performing less than 8 ALPPS operations were considered low volume, others high volume. This cutoff was based on the median number of cases per center (n = 8). Data on patient demographics, tumor type, comorbidities, volumetry, procedure details, pathology, complications, survival, and recurrence were provided by participating centers. Volumetric data were entered on the basis of imaging performed in each center, and FLR volume is reported with tumors in the FLR subtracted. To adapt liver volumes to metabolic demand, standardized total liver volume was calculated.[14] To standardize kinetic growth, a mean volume increase per day was calculated assuming a linear growth model. Growth was expressed in cubic centimeter per day and standardized future liver remnants (sFLR) increase per day in percent.

Main outcome was 90-day mortality. Complications were recorded using the Clavien-Dindo classification.[15,16] We defined severe complications as a complication grade of IIIb or greater as in previous publications.[15,17] Severe complications require general anesthesia for intervention and also include mortality. To enable comparative analyses, we also analyzed complications of grade IIIa or greater, because this was used in other studies also including interventions performed without general anesthesia.[18] Further outcome parameters included in-hospital mortality, 30-day mortality, overall complications, postoperative liver and renal failure, and intensive care unit and length of hospital stay. Postoperative liver failure was defined according to the 50/50 criteria,[19] renal failure as increase of creatinine within 48 hours after surgery to more than 1.4 times of the preoperative level.[20]

Bias and Study Size

All patients enrolled into the registry, except for those lacking information about the procedure and 90-day survival status, were included. Centers were encouraged to enter all cases of ALPPS performed and not select patients on the basis of any criteria, specifically outcome. Centers were contacted to confirm that they had entered all ALPPS cases performed in their respective center and to complete the 90-day survival status.

Quantitative Variables and Statistical Methods

The distribution of variables was analyzed using the Kolmogorov-Smirnov test, and data are expressed using means and standard deviation (SD) for normally distributed and median and interquartile ranges for nonnormally distributed data. Uni- and multivariate linear and binary logistic regression analyses were performed for severe complications including death during hospitalization (≥grade IIIb). Data were reported as point estimates (odds ratios) with 95% confidence intervals. *P* values less than 0.05 were considered as significant. Logistic regression analysis was performed for a kinetic growth rate less than 0.02 per day. Kaplan-Meier method was used for survival and recurrence-free survival. All statistical analyses were performed using SPSS version 22 for Mac (IBM Corp., Armonk, NY).

RESULTS

Characteristics of Participants

Ninety-nine centers registered with the ALPPS registry, of which 56 entered 255 patients undergoing ALPPS. Supplemental Digital Content Figure 1, available at http://links.lww.com/SLA/A620, shows exclusion of patients due to incomplete data. A total of 202 patients from 41 centers provided complete data sets of procedures and 90-day survival status. Demographics are summarized in Table 1. In 70% of patients, the indication for ALPPS was colorectal liver metastases (CRLM). Ten centers (25%) performed more than 8 procedures. Details on patients with CRLM are given in Supplemental Digital Content Table 1, available at http://links.lww.com/SLA/A619.

Operative Characteristics

As presented in Table 2, 4 cases in the registry were performed laparoscopically and 1 with the assistance of a robot. None of these 5 cases had postoperative complications of IIIb or greater, and all survived 90 days. One laparoscopically resected patient died after 181 days with complications from the resection of the primary colonic tumor.

The different types of ALPPS performed are shown in Supplemental Digital Content Figure 2, available at http://links.lww.com/SLA/A620. The median sFLR size of the *right hepatectomy ALPPS* (A), the *right trisectionectomy ALPPS + segment* 1 (B), and the *right trisectionectomy ALPPS − segment* 1 (C) was 0.25, 0.20, and

TABLE 1. Main Characteristics of 202 Patients in the ALPPS Registry

Variable of Interest	All Patients (n = 202)
Age, median (IQR), yr	60 (53–68)
Sex, male/female, number (%)	121/81(60%/40%)
Ethnic origin	
White, n (%)	188 (93)
Asian, n (%)	10 (5)
Other*, n (%)	4 (2)
Tumor type	
CRLM, n (%)	141 (70)
HCC, n (%)	17 (8)
PHCC, n (%)	11 (5)
IHCC, n (%)	8 (4)
NET, n (%)	8 (4)
Gallbladder cancer, n (%)	6 (3)
Others, n (%)	11 (5)
Charlson Index (1–14)†, median (IQR)	8 (6–9)
Histological abnormalities, data available (100%)	n = 150 (100%)
Abnormal liver histology (fibrosis/steatosis/chemotherapy-related changes), n (%)	79 (52)
Location of ALPPS patients	
Total centers (no. centers registered)	75
Total (no. patients/no. centers)	202/41
Europe (no. patients/no. centers)	136/27
South America (no. patients/no. centers)	43/4
North America (no. patients/no. centers)	13/4
Asia (no. patients/no. centers)	9/5
Middle East (no. patients/no. centers)	1/1
Year in which ALPPS was performed	
2011, n (%)	28 (14)
2012, n (%)	112 (55)
2013, n (%)	62 (30)
Low- and high-volume centers	
<8 procedures, no. patients/no. centers	75/31
≥8 procedures, no. patients/no. centers	127/10

"Data available" refers to the number of patients in the registry with complete information about the respective variable.

*Other include 3 African patients and 1 Indian patient.

†Charlson Index is a validated method to quantify comorbidities.

CRLM indicates colorectal liver metastasis; HCC, hepatocellular carcinoma; IHCC, intrahepatic cholangiocarcinoma; IQR, interquartile range; NET, neuroendocrine tumor; PHCC, perihilar cholangiocarcinoma.

TABLE 2. Main Operative Characteristics of 202 Patients in the ALPPS Registry

Variable	All Patients (n = 202)
Laparoscopic/robotic ALPPS, n (%)	5 (3)
Type of ALPPS*	
Right hepatectomy ALPPS, n (%)	106 (52)
Right trisectionectomy ALPPS + Sg 1, n (%)	69 (34)
Right trisectionectomy ALPPS − Sg 1, n (%)	17 (8)
Other types†, n (%)	10 (5)
Mean operative time ALPPS stage I, minutes, mean (SD)	327 (±119)
Mean operative time ALPPS stage II, minutes, mean (SD)	156 (±75)
Pringle maneuver, data available	n = 134 (100%)
Performed in n (%) of cases	65 (49)
Cumulative time performed, minutes, median (IQR)	30 (16–45)
CVP, data available	n = 68 (100%)
mm Hg, median (IQR)	5 (3–6)
Blood loss ALPPS stage I, data available	n = 159 (100%)
<100 mL, n (%)	23 (14)
101–600 mL, n (%)	77 (48)
601–1000 mL, n (%)	35 (22)
>1000 mL, n (%)	24 (15)
Blood loss ALPPS stage II, data available	n = 145 (100%)
<100 mL, n (%)	60 (41)
101–600 mL, n (%)	67 (46)
601–1000 mL, n (%)	10 (7)
>1000 mL, n (%)	8 (6)
RBC transfusion ALPPS stage I	n = 189 (100%)
Patients transfused, n (%)	53 (28)
Units of RBC, median (IQR)	3 (2–4)
RBC transfusion ALPPS Stage II, data available	n = 184 (100%)
Patients transfused, n (%)	44 (24)
Units of RBC, median (IQR)	2 (2–3)

"Data available" refers to the number of patients in the registry with complete information about the respective variable.

*For type of ALPPS, see Supplemental Digital Content Figure S2, available at http://links.lww.com/SLA/A620.

†Other types include single segment ALPPS and left ALPPS as shown in Supplemental Digital Content Figure S3, available at http://links.lww.com/SLA/A620.

ALPPS indicates Associating Liver Partition With Portal Vein Ligation for Staged Hepatectomy; CVP, central venous pressure; IQR, interquartile range; RBC, red blood cells; Sg, segment.

0.19, respectively. Five ALPPS procedures with single segment FLRs and 1 left hepatectomy ALPPS were reported (Supplemental Digital Content Fig. 3, available at http://links.lww.com/SLA/A620). In 12% of patients, additional extrahepatic procedures were simultaneously performed, mainly resections of colorectal primaries during stage I (Supplemental Digital Content Table 2, available at http://links.lww.com/SLA/A619).

Biometric Changes of Liver Volumes

Mean weight, height, body surface area (Mosteller formula), body mass index, and liver volumes are shown in Supplemental Digital Content Table 3, available at http://links.lww.com/SLA/A619. Median starting FLR before stage I was 337 cm^3 corresponding to an sFLR of 0.21. Between stage I and II, the volume increased by 80% (IQR 49%–116%) within a median time interval of 7 days (interquartile range: 6–13 days) to a volume before stage II of 612 cm^3 (468–720 cm^3), corresponding to an sFLR of 0.40 (0.31–0.47).

Postoperative Outcomes

As shown in Table 3 both ALPPS stages were completed in 98% (197/202) of patients. Complications are shown in Table 3 and details are listed in Supplemental Digital Content Table 4, available at http://links.lww.com/SLA/A619. Considering both stages, 28% of patients experienced severe complications including mortality (grade ≥IIIb). Perioperative 90-day mortality was 9%. Significant risk factors for severe complications were red blood cell transfusion [odds ratio (OR), 5.26], duration of stage I surgery greater than 300 minutes (OR, 4.42), age greater than 60 years (OR, 3.76), and non-CRLM (OR, 2.73) (Fig. 1A). Severe complication rate was higher in patients with primary liver cancer than in those with CRLM (Fig. 1B). Patients with CRLM aged 60 years and younger had a severe complication rate of 16% and a 90-day mortality of 5.1%, both reflecting significantly better results in comparison with others (Fig. 1C). Length of intensive care unit and hospital stay after each stage are given in Supplemental Digital Content Table S4, available at http://links.lww.com/SLA/A619.

Survival

Overall survival of patients undergoing ALPPS at 1 and 2 years was 73% and 59%, respectively (Fig. 2A). Patients with CRLM younger than 60 years had better survival than those with non-CRLM or age more than 60 years (Figs. 2B, C). The combination of age less than 60 years and CRLM showed better survival than all others (Fig. 2D). An estimate of the proportion of patients surviving each tumor type including numbers at risk is given at 1 and 2 years, if available (Table 4).

Predictors of Hypertrophy

The results of the multivariate analysis for factors impacting on kinetic growth are shown in Supplemental Digital Content Figure 4A,

TABLE 3. Main Postoperative Outcomes of 202 Patients in the ALPPS Registry

Variable	All Patients (n = 202)
Failure to reach stage II, n (%)	5 (2)
30-d mortality, n (%)	5 (2)
In-hospital mortality, n (%)	18 (9)
90-d mortality	
In all patients n (%)	19 (9)
In CRLM, n (%) (no. total CRLM)	11 (8%) (n = 141)
In HCC, n (%) (no. total HCC)	2 (12%) (n = 17)
In PHCC, n (%) (no. total PHCC)	3 (27%) (n = 11)
In IHCC, n (%) (no. total IHCC)	1 (13%) (n = 8)
In NET, n (%) (no. total NET)	0 (0%) (n = 8)
In gallbladder cancer (%) (no. total gallbladder cancer)	2 (33%) (n = 6)
In subgroup ≤60 yr + CRLM, n (%), (no. total)	4 (5.1%) (n = 78)
Highest complication ≥grade IIIa in both stages	
All patients, n (%) (no. total)	80 (40%) (n = 202)
In CRLM group, n (%) (no. total)	51 (36%) (n = 141)
In subgroup ≤60 yr + CRLM, n (%) (no. total)	23 (29%) (n = 78)
Highest complication ≥grade IIIb in both stages	
All tumor types, n (%)	56 (28%) (n = 202)
In CRLM group, n (%), (no. total)	30 (21%) (n = 141)
In subgroup ≤60 yr + CRLM, n (%) (no. total)	12 (16%) (n = 78)

Grading of complications according to Clavien-Dindo classification.

CRLM indicates colorectal liver metastasis; HCC, hepatocellular carcinoma; IHCC, intrahepatic cholangiocarcinoma; NET, neuroendocrine tumor; PHCC, perihilar cholangiocarcinoma.

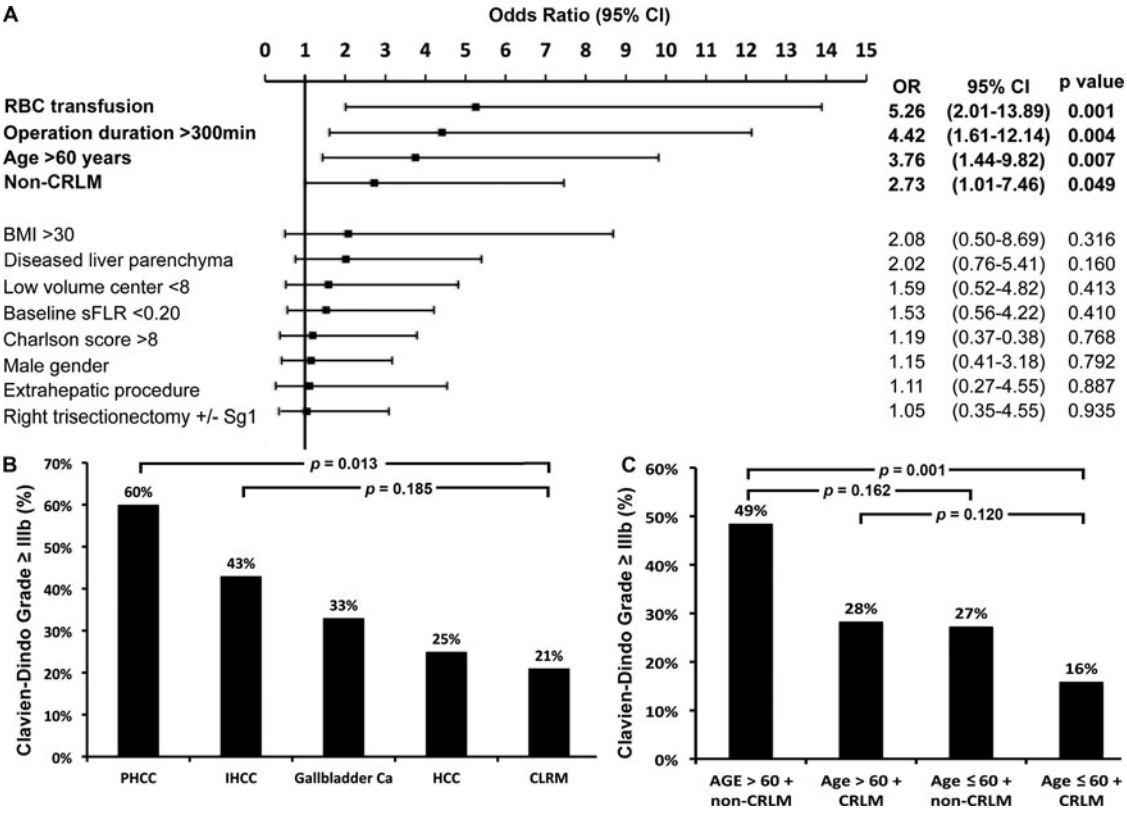

FIGURE 1. A, Logistic regression analysis for severe complications and mortality (≥IIIb-V). "Operation duration" refers to ALPPS stage I. B, Rate of severe complications and mortality for different tumor types. C, Rate of severe complications and mortality for patients older than 60 years/60 years and younger, with the diagnosis of CRLM/non-CRLM. BMI indicates body mass index; Ca, carcinoma; CI, confidence interval; CRLM, colorectal liver metastasis; HCC, hepatocellular carcinoma; IHCC, intrahepatic cholangiocarcinoma; OR, odds ratio; PHCC, perihilar cholangiocarcinoma; Sg, segment.

available at http://links.lww.com/SLA/A620. Age greater than 60 years, use of the Pringle maneuver, and diseased liver parenchyma (steatosis, fibrosis, chemotherapy-related changes) were significant factors for reduced kinetic growth (<0.02 FLR per day). The associations of these factors and reduced kinetic growth are summarized in Supplemental Digital Content Figures 4B–D, available at http://links.lww.com/SLA/A620.

DISCUSSION

The first analysis of the International ALPPS registry presents the currently largest studied population of ALPPS patients. The 90-day mortality after ALPPS was 9%, and independent predictors for severe complications during hospitalization were tumors other than CRLM, age greater than 60 years, and 2 markers of complex liver resections: need for intraoperative red blood cell transfusions and stage I operations for more than 5 hours. Based on these findings, we postulate that the observed elevated complication rate may be attributable to both indications beyond CRLM and technical challenges of ALPPS. The subgroup analysis revealed that patients with CRLM younger than 60 years had significantly lower complication rates.

Although the large and multicenter study population of 202 patients represents the strength of this study, the shortcomings are the inhomogeneity of the study population including patients with all types of liver tumors and study centers with high and low volumes. This is inherent in the study design due to the novelty of the procedure. Another limitation is the incompleteness of data in some areas such as laboratory values, which is likely related to the effort required for the data entry. Also, data could not be verified by physical monitor visits. Instead, weekly monitoring was performed through a query and answer system, e-mails, and phone calls from the study center in Zurich. Despite these limitations, this analysis currently represents the best available data on ALPPS.

One central finding is the impressive hypertrophy of 80% within a median of 7 days. This observation remains a robust phenomenon across the experience with 178 patients with complete volumetric data sets. The median kinetic growth of 0.02 sFLR (interquartile range: 0.01–0.03) provides the basis for the estimation of the required time period for volume hypertrophy in ALPPS: for example, a patient with a starting FLR of 15% has a 75% change to reach the volume cutoff of 30% sFLR within 15 days after stage I. The finding that Pringle maneuver and diseased liver are independently associated with inferior FLR growth is consistent with experimental studies showing that that warm ischemia and, for example, steatosis reduce the regenerative capacity of rodent livers after resection.[21,22]

Although there is a consensus that standard liver resections have a perioperative mortality of up to 3% in experienced centers,[16,23] the mortality of complex liver resections is rarely reported and likely to stand in the vicinity of 5% to 8%.[1,18,24] However, reports on case series of ALPPS have mentioned higher perioperative mortality rates ranging between 12% and 28%.[2,5,6,25]

Kokudo and Shindoh[13] recently made a call for a phase I process before taking the next step to confirm the safety of the ALPPS by providing an acceptable morbidity and mortality rate comparable with

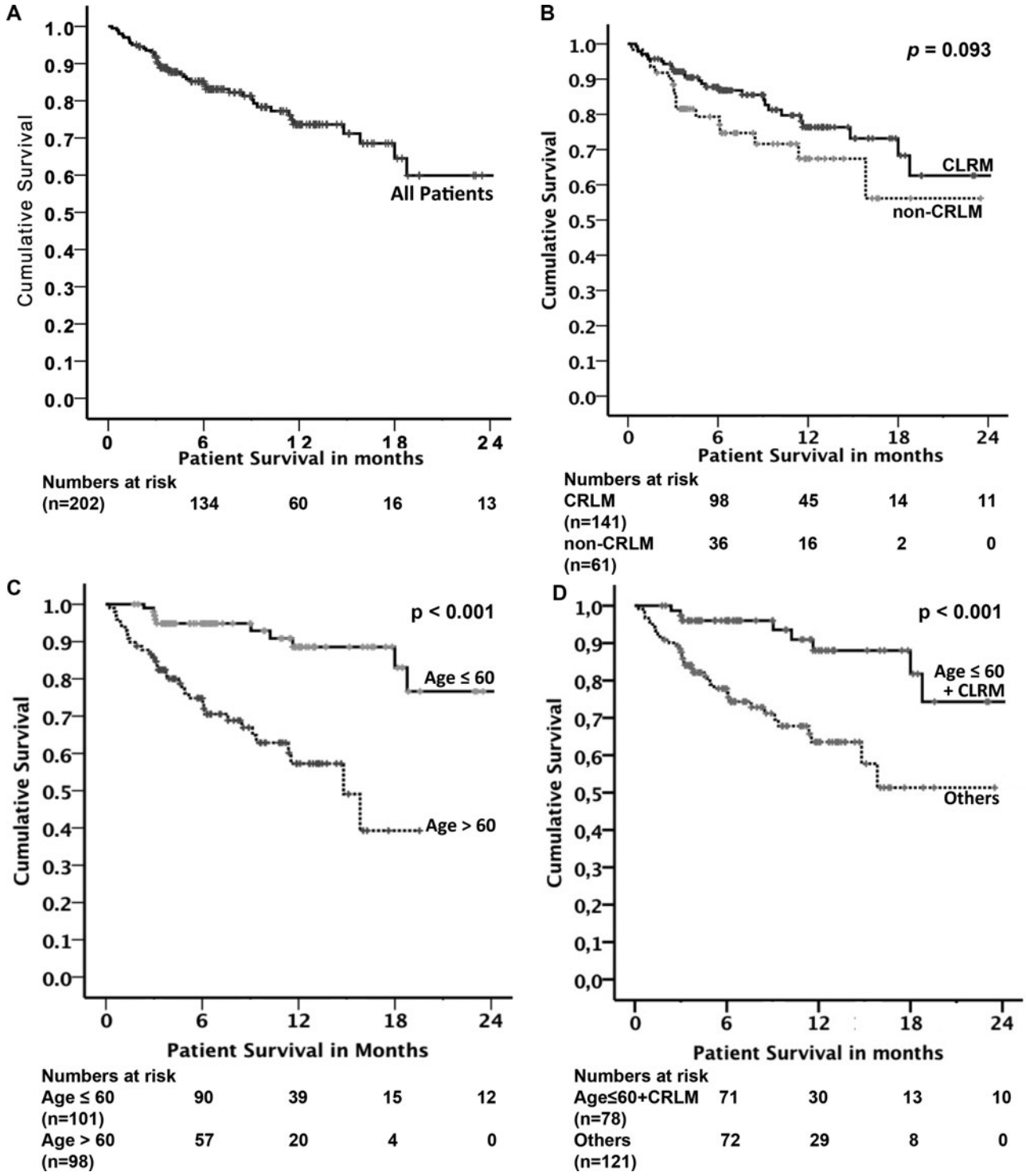

FIGURE 2. Survival in ALPPS patients. A, Overall survival of ALPPS patients. B, Difference in survival for CRLM versus non-CRLM. C, Difference in survival in patients with age greater than 60 years and 60 years and younger. D, Difference in survival in patients with CRLM and age greater than 60 versus all others.

TABLE 4. Survival and Disease-Free Survival in 202 Patients in the ALPPS Registry

Patients According to Tumor Type	All Patients (n = 202)
All patients	202
R-status available	n = 185 (100%)
Incomplete resection (R1/R2), n (%)	16 (9)
Median follow-up, mo (IQR)	9 (6–13)
Median survival, mo	25
Survival at 1 yr (patients at risk)	73% (52)
Survival at 2 yr (patients at risk)	59% (5)
Median disease-free survival, mo	14
Disease-free survival at 1 yr (patients at risk)	60% (27)
Disease-free survival at 2 yr (patients at risk)	42% (1)
CRLM, no. patients	141
R-status available	n = 130 (100%)
Incomplete resection (R1/R2), n (%)	12 (9)
Survival at 1 yr* (patients at risk)	76% (41)
Survival at 2 yr* (patients at risk)	62% (6)
Disease-free survival at 1 yr* (patients at risk)	59% (28)
Disease-free survival at 2 yr* (patients at risk)	41% (9)
Subgroup <60 yr + CRLM only, number of patients	78
R-status available	n = 73 (100%)
Incomplete resection (R1/R2), n (%)	6 (8)
Disease-free survival at 1 yr* (patients at risk)	55% (17)
Disease-free survival at 2 yr* (patients at risk)	36% (7)
Survival at 1 yr* (patients at risk)	88% (33)
Survival at 2 yr* (patients at risk)	74% (10)
HCC, no. patients	17
R-status available	n = 15 (100%)
Incomplete resection (R1/R2), n (%)	0
Disease-free survival at 1 yr* (patients at risk)	87% (1)
Survival at 1 yr* (patients at risk)	61% (1)
PHCC, no. patients	11
R-status available	n = 9 (100%)
Incomplete resection (R1/R2), n (%)	2 (22)
Disease-free survival at 1 yr*	NA†
Survival at 1 yr*	NA†
IHCC, no. patients	8
R-status available	n = 7 (100%)
Incomplete resection (R1/R2) in %	1 (14%)
Disease-free survival at 1 yr* (patients at risk)	31% (1)
Survival at 1 yr* (patients at risk)	73% (1)
NET, no. patients	8
R-status available	n = 8 (100%)
Incomplete resection (R1/R2), n (%)	1 (13)
Disease-free survival at 1 yr* (patients at risk)	83% (5)
Survival at 1 yr* (patients at risk)	73% (1)
Gallbladder cancer, no. patients	6
R-status available	n = 6 (100%)
Incomplete resection (R1/R2), n (%)	0
Disease-free survival at 1 yr*	NA†
Survival at 1 yr*	NA†

*Cumulative proportion surviving at the time according to Kaplan-Meier estimates.
†Not available: follow-up not long enough to assess.
CRLM indicates colorectal liver metastases; HCC, hepatocellular carcinoma; IHCC, intrahepatic cholangiocarcinoma; IQR, interquartile range; NET, neuroendocrine tumor; PHCC, perihilar cholangiocarcinoma.

current clinical practice. What constitutes an "acceptable" perioperative morbidity/mortality rate remains arguable, because it is difficult to identify a population that matches ALPPS patients.[25] Parameters such as tumor load and type and FLR size should be similar when patients with ALPPS are compared with patients with conventional 2-stage procedures. A recently published study from the MD Anderson group comparing portal vein embolization (PVE) and staged hepatectomy from their own institution (n = 141) with the inaugural ALPPS series from Germany (n = 25) demonstrated a lower rate of complications of grade III or greater (33% vs 40%) and 90-day mortality (6% vs12% for the PVE cohort, although the difference did not reach statistical significance).[26] The figure of grade IIIa of 40% or greater from the inaugural ALPPS series is consistent with this registry analysis, in which 42% of the patients developed a grade IIIa or higher complication. The main issue with the MD Anderson study is the lack of comparability of groups. For example, 78% (n = 112) of the 144 patients in the PVE cohort underwent only an interventional embolization, followed by a curative resection without the need for two hepatectomies. This was possible only because those patients did not require a "cleaning" of the FLR, which is a common feature of most ALPPS patients. ALPPS patients receiving 2 operations have obviously a higher risk for more complications. On the contrary, as we have shown recently, patients undergoing ALPPS have a higher chance to achieve complete tumor resection despite having more complications.[25] The benefit of achieving complete resection has to be weighed against the risk of complications of more extensive procedures. A conclusive comparison of the PVE cohorts with ALPPS cohorts with mixed tumors is difficult.

The next step forward is to explore efficacy of ALPPS in an randomized controlled trial (RCT).[27] To be on the safer side, a definition of inclusion criteria is key to establish a definitive role for ALPPS. ALPPS should be randomly compared with other types of 2-stage approaches including PVE and PVL with cleaning of the FLR. Such a study ought to be limited to patients, who have shown similar outcome in the registry when compared with historical series of conventional 2-stage hepatectomy. The subgroup of patients younger than 60 years with CRLM in the registry not only has similar tumor characteristics of CRLM but also perioperative outcome comparable with the largest reported series of 2-stage hepatectomies for CRLM (n = 65),[18] including a 90-day mortality rate of 5.1 versus 6.4%, respectively. An important drawback of the conventional approach, as also documented in our previous comparative analysis,[25] is that only about two-thirds of patients reached stage II,[18] whereas 98% of the patients were offered stage II in the ALPPS registry. This finding is likely to have a major impact an intent-to-cure analysis in an RCT. Only a prospective randomized controlled trial would make a conclusive risk benefit analysis for ALPPS possible.

Another important finding of the registry is that patients with cholangiocarcinoma and gallbladder cancer had an inferior outcome, which is similar to previously reported case series.[4,5,9,28] It is a weakness of this study that this group comprises only 25 of 202 patients (12%). It is, however, fair to conclude that ALPPS should be performed with great caution in this population. It seems that ALPPS might have been overused in elderly patients with extensive disease burden of liver tumors, specifically primary hepatic tumors, as a "magic bullet" by clinicians during the early phase of enthusiasm about rapid hypertrophy. It was tempting to speculate that the "auxiliary liver" in place after stage I would allow any extent of liver resection in elderly patients with comorbidities otherwise prohibitive.

Information on long-term survival after ALPPS is sparse due to low numbers of patients in single center series, the heterogenous population regarding the type of tumors, and its recent introduction.[2] ALPPS patients with CRLM have a 1- and 2-year survival of 88% and 74%, respectively, and a median survival of 24 months. These

figures compare favorably with the MD Anderson CRLM 2-stage cohort with a 3-year survival of 67%.[18] The survival of patients with CRLM younger than 60 years was significantly better than that of other subgroups. ALPPS is a physiologically challenging operation, and elderly patients seem to be doing worse both perioperatively and as far as medium-term survival are concerned. Survival data on other indications than CRLM are inconclusive at this point due to the low number of patients.

Beside patient survival, disease-free survival (DFS) is another key parameter in assessing the oncological value of ALPPS. To our knowledge, this is the first report on DFS after ALPPS. There is still a paucity of data on DFS in patients with CRLM, who undergo conventional 2-stage hepatectomy. In a 2-center study including 35 patients, DFS after 2-stage hepatectomy for CRLM was 85% and 68% at 1 and 2 years, respectively.[24] In a larger cohort,[18] the rate of DFS of those patients, who completed the second stage (n = 47), reached 39% at 1 year and 20% at 3 years.[18] Again, these studies do not report DFS in an intent-to-cure analysis but only in patients, who underwent both stages. In comparison, the 1- and 2-year DFS in the ALPPS registry for patients with CRLM of 59% and 41%, respectively, with a median DFS of 14 months, seems acceptable, particularly considering that almost all patients could eventually benefit from a curative resection. The concern raised on the basis of small data sets about high tumor recurrence after ALPPS seems currently unwarranted.[11,29]

Another interesting finding of the registry analysis was that intraoperative red blood cell transfusion requirements and long operative time during stage I were independent factors for more complications. These findings may point to the technical complexity of ALPPS. Improvements of outcomes with ALPPS should, therefore, be expected not only from more restrictive indications but also from technical refinements. There are too few laparoscopic cases reported in the registry to draw any firm conclusions.

CONCLUSIONS

The analysis of the first 202 patients of the international ALPPS registry shows feasibility of ALPPS with a progression of the stage II of 98% and an overall mortality of 9%. In patients with CRLM younger than 60 years, however, an outcome comparable with conventional 2-stage hepatectomies may be expected. To move forward, a randomized trial using strict inclusion criteria should be performed.

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DISCUSSANTS

F. R. Pruvot (Lille, France):

Congratulations to Dr. Schadde and Pierre Alain Clavien, and thank you to the ESA committee for giving me the privilege to discuss this very relevant article.

Briefly, ALPPS has emerged as a new procedure to, first, bypass insufficient remnant volume and, second, to shorten the time interval within a two-stage resection. Immediately, the question has been raised, pertaining to its efficacy on remnant hypertrophy, mortality, morbidity, and, of course, impact on survival. Although some data are missing, the article provides answers to most questions and is an essential step before ALPPS becomes a standard procedure, with rates of 9% of mortality, 27% of severe morbidity, and a focus on CRLM.

I would like to make two preliminary comments:

First, the choice of the methodology used, rendering it a prospective ongoing study rather than a randomized trial comparing ALPPS to a classical resection, is correct. I think that it will be difficult to set up a randomized trial and choose which classical resection arm is the best—portal embolization with a 1-stage curative resection or a 2-stage with portal embolization during interval; uni or bilateral lesions? Second, which is more efficient, choosing ALPPS by principle, or rescue-ALPPS, after a lack of postembolization

hypertrophy, or finally an intraoperative decision for ALPPS? For example, what would you do, if a patient would clearly benefit from ALPPS hypertrophy after embolization as he has been included within classical arm? In an intention to treat, randomization could give some ethical trouble.

Second, only 3 French centers have contributed to the registry. For, in February 2013, as the actual president of the French HPB association, I proposed analyzing them in a multicentric survey of ALPPS. Sixty two French patients were analyzed, who now make up more than 75 to be later added to the international registry.

I have 1 question concerning the methodology:

Do you favor the "classical" standardized volumetry calculation, instead of the "remnant to body weight ratio"? As you know, the ratio of body weight was the methodology used by Schnitzbauer in the initial ALPPS report. This ratio to body weight is more accurate, especially in very low volumes. In your series, in which the range of the baseline remnant volume in the standardized calculation was between 17% and 27%, which is on both side of the classical cutoff 20% to 25%; remnant volume of the body weight ratio was calculated as below 0.5% for all. Furthermore, in your series, I could notice a high proportion (44%) of simple right-hepatectomies, a resection that usually gives a sufficient remnant volume. Could you comment on this?

I have 3 questions concerning the results:

Apparently no postoperative factor was significant for morbimortality. In our French multicentric series, infected and/or bilious peritoneal fluid at stage 2 was the only predictor of Clavien type 3 or more, by multivariate analysis. Did you also analyze these data?

You did not find that the future liver remnant at baseline was a significant parameter for morbidity, but, how about kinetic growth? In other words, independently from baseline value, is a slow kinetic growth needed to postpone stage 2, or should we use liver scintigraphy to estimate liver function?

The decision to use ALPPS, instead of performing a classical portal embolization and a 1- or 2-stage resection, is mainly preoperative. However, 2 of the 3 significant multivariate factors for predicting ALPPS morbidity are intraoperative ones, that is, the transfusion and operating time. This is comparable with 2 of the 3 significant factors for a lack of hypertrophy, namely, the use of the Pringle maneuver, the quality of the liver parenchyma (usually difficult to assess preoperatively). So, in these conditions, how would you preoperatively estimate the risks of ALPPS, in comparison with a classical strategy?

Finally, I have 2 questions concerning the indications and strategy:

Taking into account the oncological principle of dissection for hilar cholangiocarcinoma may be conflicting with the transection of ALPPS; do you think ALPPS is contraindicated in the resection of bile duct tumors?

Finally, ALPPS had a 3.76 odd ratio for more severe morbidity in patients older than 60 years. Is an age of more than 60 years a contraindication for ALPPS?

Once again, thank you for your essential work. It is a major contribution in the field of HPB surgery.

Response From E. Schadde (Zurich, Switzerland):

Thank you for these questions, Professor Pruvot. First, with regard to the volumetry question, we gave the data on the liver-remnant-to-body weight ratio as well in the article. We did use the sFLR, as it is done by the MD Anderson group, but we provided all the parameters that we could. Your question about the simple right hepatectomy is important because the majority of ALPPS cases in the study turned out to be "ALPPS" right hepatectomies. However, when you look at the low FLR volumes, you will see that these were not normal right hepatectomies; the low volumes were due to large tumor resections within the future liver remnant, which led to really extensive removals of liver parenchyma but were formally classified by the surgeons entering them, correctly, as right hepatectomies, because the transection went along Cantlie line.

With regard to your second question about the infected fluid, we did not collect data on the infected fluid. When we initiated the registry, which we actually did simultaneously with the preparation of the randomized trial, we did not think of this. So, we have no entries about culture results. I do have results from Zurich, but they are just a small subgroup of the analysis, and there are not enough events to use them as an endpoint in a multivariate analysis.

Your third question regards kinetic growth and, more specifically, whether it is a risk factor. Using complications greater than 3B as an endpoint, we could not identify kinetic growth as a risk factor. But, what was interesting was the low baseline FLR before stage II, which you addressed in the next question. This is a risk factor for liver failure, which does not appear in the article, because we are currently analyzing the entire series with different endpoints. We do find that low baseline FLR before a stage II resection is a risk factor for liver failure. So, we could advise surgeons to be generous with the volume before stage II, when performing ALPPS.

In terms of what to do with the fact that Pringle and the quality of the liver parenchyma are risk factors for kinetic growth still needs to be found. Does Pringle really reduce the speed of kinetic growth between the 2 stages? This is, indeed, questionable, but this is what the multivariate analysis suggested. The role of the quality of the liver parenchyma, on the contrary, did not surprise us, and this can be well assessed preoperatively.

Your next question is an important one: Is ALPSS contraindicated in Klatskin tumors? It is difficult for a surgeon to tell other surgeons that a type of tumor is a contraindication for ALPPS; there have been successful cases performed. However, as you know from the literature, the German group in Tübingen has also published a series on patients, operated with Klatskin tumors, with high morbidity and mortality rates; they were extremely concerned about the patients with transhepatic drains due to cholestasis before ALPPS. We should be very cautious with these patients because many, who have explored ALPPS in this area, have either had mortalities or severe morbidities in this patient population. The Tübingen group concluded that it is best to avoid ALPPS in patients with cholestasis and biliary drains, but we cannot support this with data, because we have not specifically analyzed how many patients had drains or how many had contaminated bile systems.

With regard to your final question about age, we are currently having this exact discussion about whether we should limit this procedure to patient younger than 60 years of age. About half of the patients in our series are older than 60 years, as generally are our patients with colorectal liver metastases. We should probably be aware that patients older than 60 years do not have much reserve for this operation, as ALPPS is physiologically a very challenging operation.

DISCUSSANTS

A. Pinna (Bologna, Italy):

Thank you for this very nice presentation. I just have 2 quick questions. First, should patients with jaundice be drained before an ALPPS procedure? Second, when you considered patients older than 60 years, do you think that they failed because of hemodynamical instability after the resection, or was the remnant liver unable to increase its functional volume? In other words, is it the age of the cells or the state of the heart that really matters?

Response From E. Schadde (Zurich, Switzerland):

Thank you, Professor Pinna, for these 2 questions. As far as patients with jaundice are concerned, I have previously addressed this question. We should be careful with patients with external biliary

drains, when performing ALPPS. Second, with regard to age, I would answer this question in a very general way. ALPPS is a physiologically challenging operation, which is more difficult to tolerate for someone, who is aged 70 years rather than 40 years. If things go wrong and you have an infection with ALPPS, when you're older than 70 years, your risk of developing a severe complication is very high. Thus, the general capability of a patient to tolerate a septic complication is what matters, whether it is due to the liver cells or the heart.

DISCUSSANTS

E. Barroso (Lisbon, Portugal):

Let me say something strong—ALPPS is the last option, or the ultimate possibility to cure some patients; it's not a new operation that you can utilize before you try to do a portal vein embolization. I think that it's not ethical to propose this kind of operation to a patient, without first proposing a portal vein embolization. Why not try performing a hepatic vein embolization, before ALPPS? Our results were presented in IHPBA, in Korea, stating that before we can consider ALPPS, after portal vein embolization, we need to try hepatic vein embolization to improve the functional liver reserve. Frequently, we avoid operating patients with the ALPPS technique. Finally, from this report, do you think that the quality of the response to portal vein embolization is also a predictor of what is going to happen with ALPPS? If the liver volume is not sufficient, after portal vein embolization, what is the criterion to propose as a last option?

Response From E. Schadde (Zurich, Switzerland):

Thank you. I will respond to your last question first. Several groups have published reports on salvage ALPPS, or when portal vein embolization does not work and ALPPS is attempted as a rescue approach. There are very few reports in total, but they show that if portal vein embolization has not worked, then ALPPS *does* work. The successful cases we have performed in Zurich and elsewhere support this. In your first question, you proposed to limit ALPPS to a salvage approach, because everything else should be used before it. There are certain technical situations, where you would prefer ALPPS, especially when you discuss this topic with those, who have much experience with this operation. We should consider portal vein embolization and portal vein ligation the standards, against which ALPPS needs to be tested. This is exactly why we propose a randomized trial.